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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,207	02/25/2002	Marlon D. Cowart	6791.US.O2	2847

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 07/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,207	COWART ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/4.3/24, 4/19*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-17,23-25,27-47,49-53,61-73,77-86,103,105-111,127,129-136,138-144,146-157 and 159-164.

Continuation of Disposition of Claims: Claims rejected are 1-17,23-25,27-47,49-53,61-73,77-86,103,105-111,127,129-136,138-144,146-157 and 159-164.

DETAILED ACTION

Applicants' response, which included cancellation of claims18-22, 26, 44, 48, 55-60, 74-76, 87-102, 104, 112-126, 128, 133, 137, 145, 158, and amendment to claims 1, 43, 49, 103, 106, 107, 127, 129, 130, 132, 134, 135, 136, 144, 151, 154, 157 filed on 4/19/2004 under 37 CFR 1.111 in reply to the Non-Final rejection has been considered and made of record.

Claims 1-17, 23-25, 27-47, 49-53, 61-73, 77-86, 103, 105-111, 127, 129-136, 138-144, 146-157 and 159-164 are now pending.

In view of applicants' response indicating that the copending application 10/044,495 has been abandoned, the obviousness-type double patenting rejection made in the previous office action has been obviated. However, the following rejections made in the previous office action are maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17, 23-25, 27-47, 49-53, 61-73, 77-86, 103, 105-111, 127, 129-136, 138-144, 146-157 and 159-164 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record. To repeat:

1. Recitation of the term "prodrug" in claims 1, 43, 103, 127, 132,136, and 144 is deemed as indefinite. Prodrugs in general and as noted in specification, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that

sense recitation of prodrug is acceptable. However, the definition of various R, groups include such groups, namely esters, amides, carbamoyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups. Thus there is an ambiguity as to when a group such as ester to be treated as prodrug group when not as prodrug group.

Applicants' traversal is not persuasive.

First of all it is not the definition of prodrug that is being addressed here. It is the ambiguity that some variable groups are also by definition appears to be prodrug. Thus given a compound of the genus with an ester or amide or carbamate as functional group, and making a prodrug thereof would result in ambiguity as which functionality is now a prodrug and which is not. In general, as noted by applicants, produrgs undergo in vivo transformation to active compound. If that is the case, the species embraced in the instant genus with an ester or amide or carbamate as functional group, could be deemed as inactive.

Thus one trained in the art would not know whether a compound is active or not if the compound has an ester or amide or carbamate as functional group,

Hence, this rejection is proper and is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 156-162 and 164 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating gastrointestinal disorders,

obesity, sleep disorder and asthma requiring histamine-3 receptor does not reasonably provide enablement for treatment all or any disease as embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to "a method of treating a disorder wherein the disorder is ameliorated by modulating histamine-3 receptor or selectively modulating the effects of histamine-3-receptors" which as recited reads on any or all disorders for which there is no enabling disclosure. The scope of the claims includes treatment of any or all of diseases, which is not adequately enabled solely based on the activity of the compounds provided in the specification at pages 29-32. The instant compounds are disclosed have histamine-3 receptor inhibitory activity and it is recited that the instant compounds are useful in treating several diseases, for which applicants provide no competent evidence. Reading specification it appears that instant compound is useful for treating all sorts of disorders/diseases including Alzheimer's disease, bipolar disorder, all cognitive disorders, septic shock etc. for which applicants have not provided any experimental support. Moreover many if not most of central nervous system diseases such as Alzheimer's disease, multiple sclerosis etc. are very difficult to treat. For multiple sclerosis alone there is no known drug, which can successfully reverse the course of the disease, despite the fact that there are many drugs which can be used for "inflammatory condition" etc. for which applicants have not provided any experimental support. Even a recent reviews of histamine-3 receptors suggest the use

of these antagonists still under experimental stage and speculative in nature. See Repka-Ramirez Curr. Allergy. Asthma Rep. 3(3): 227-31, 2003 and Barocelli et al. Pharmacol. Res. 47(4): 299-304, 2003 (PubMed Abstract provided). Even the references cited in the Information Disclosure Statement, at the time of the instant invention suggest use of these antagonists still under experimental stage and speculative in nature. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The state of the art is indicative of the requirement for undue experimentation.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating diseases that require histamine-3 receptor inhibitory activity.

2) The state of the prior art: A very recent publication expressed that the histamine-3 receptor inhibitors are still in experimental stage.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the therapeutic effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show preventive effect and the state of the art is that the effects of histamine-3 receptor antagonists are unpredictable.

6) The breadth of the claims: The instant claims embrace treatment of several diseases.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards

'preventing' the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

This rejection is same as made in the previous office action. Applicants' traversal to overcome this rejection is persuasive. Following apply.

First of all, although applicants' have provided a number non-patent literature some of which were found in a earlier search by the examiner, the y all appear to be general studies of the said receptor and applicants have not pointed out and discussed which of the references show enablement of all the diseases embraced in these claims.

Secondly, applicants have not provided any argument why the applied prior art references at the time of the invention are not applicable as to the issue of enablement of all diseases embraced in the claims. Note the prior art implies that at the time of the invention, the art ha not advanced to treat all the diseases embraced in the instant invention. Hence this reaction is deemed as proper and is maintained.

Information Disclosure Statement

References cited in the Information Disclosure Statements (paper dated 6/4/2002, 3/24/2003, 4/19/2003) are made of record.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (703) 308-4716.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

V. Balasubramanian
Venkataraman Balasubramanian

06/25/2004